



# Loss of Consciousness at Onset of Aneurysmal Subarachnoid Hemorrhage is Associated with Functional Outcomes in Good-Grade Patients

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**■ BACKGROUND:** Transient loss of consciousness (LOC) is one of the most common presentations of aneurysmal subarachnoid hemorrhage (SAH) and may be an indicator of early brain injury. In this study, we examined the association of LOC and functional outcomes in patients with good-grade SAH.

**■ METHODS:** We searched the Subarachnoid Hemorrhage International Trialists Repository for patients who presented with LOC at ictus of SAH. A propensity score analysis was performed on good-grade patients (defined as World Federation of Neurosurgical Societies grade 1–3) to balance selected covariates between those with and without LOC. The primary outcome was Glasgow Outcome Score (GOS) at 3 months (with poor outcome defined as a GOS of 1–3). Secondary outcomes were delayed cerebral ischemia (DCI), rebleed, length of hospital stay, and time to death.

**■ RESULTS:** A propensity score-matching algorithm identified 336 patients (168 with and 168 without LOC at ictus). The proportion of patients with poor functional outcome at 3 months was significantly higher in the cohort with LOC at ictus compared with the matched cohort without LOC at ictus (30% vs. 19%;  $P = 0.02$ ). There was a nonsignificant trend toward greater mortality in the patients with LOC at ictus (19% vs. 13%;  $P = 0.14$ ). There were no significant

differences in the secondary outcomes between the 2 cohorts.

**■ CONCLUSIONS:** LOC at ictus of SAH is associated with a higher rate of unfavorable functional outcomes but not of mortality, DCI, or rebleed in patients with good-grade SAH. Future studies should further investigate the putative mechanisms through which LOC mediates early brain injury in SAH.

## INTRODUCTION

Intracranial aneurysmal rupture, the most common cause of nontraumatic subarachnoid hemorrhage (SAH), carries a mortality rate as high as 67% in the first few months after rupture.<sup>1</sup> A significant proportion of the patients who do survive are left with significant disability and loss of independence. Almost 30% of survivors have moderate to severe disabilities afterward, and approximately 65% never return to the same quality of life that they enjoyed before SAH.<sup>2</sup> Prognostication in SAH is essential, influencing clinical decisions on initial management, monitoring, and duration of stay in the intensive care unit. Known prognostic factors associated with worse outcome include, but are not limited, to increasing patient age, worsening neurologic grade, ruptured posterior circulation

## Key words

- Loss of consciousness
- Subarachnoid hemorrhage

## Abbreviations and Acronyms

**BRANT:** British Aneurysm Nimodipine Trial  
**CI:** Confidence interval  
**CPP:** Cerebral perfusion pressure  
**DCI:** Delayed cerebral ischemia  
**GOS:** Glasgow Outcome Scale  
**H&H:** Hunt and Hess  
**ICP:** Intracranial pressure  
**LOC:** Loss of consciousness  
**OR:** Odds ratio  
**SAH:** Subarachnoid hemorrhage  
**SAHIT:** Subarachnoid Hemorrhage International Trialists  
**WFNS:** World Federation of Neurosurgical Societies

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aneurysm, larger aneurysm size, more subarachnoid blood detected radiographically, presence of intraventricular and/or intracerebral hemorrhage, and presence of comorbidities, including hypertension, myocardial infarction, liver disease, or previous SAH.<sup>3,4</sup>

Loss of consciousness (LOC) is one of the most common presenting symptoms in aneurysmal SAH and has been associated with worse clinical grade, larger hemorrhages, global cerebral edema, poor outcomes, and delayed cerebral ischemia (DCI).<sup>5-8</sup> The largest study of LOC in SAH was reported in 2016 by Suwatcharakoon et al.,<sup>6</sup> who retrospectively analyzed a prospective series of 1460 patients with spontaneous SAH. An important question that arose was in regard to how to separate the effect of LOC from the patient's presenting neurologic grade, using the Hunt and Hess (H&H) or World Federation of Neurosurgical Societies (WFNS) grading system.<sup>5</sup> Since high-grade patients (H&H 4–5; WFNS 4–5) have LOC by definition, it may be of value to assess LOC in otherwise low-grade patients to better assess its contribution to outcome after aneurysmal SAH. This is also of particular importance in determining the association between LOC and DCI following SAH.

Therefore, we aimed to examine the prognostic significance of LOC in patients with SAH, particularly in patients with good neurologic grade in terms of functional outcome, mortality, and SAH-associated complications, including DCI.

## METHODS

### Study and Patient Selection

We conducted our data search using the Subarachnoid Hemorrhage International Trialists (SAHIT) Repository, a combined database of recent clinical trials and prospective patient data from institutions worldwide on the topic of aneurysmal SAH.<sup>9,10</sup> The SAHIT Repository has provided data for a number of previous studies of SAH.<sup>9-14</sup> Our search included all studies in the repository. Our inclusion criteria were as follows: 1) good neurologic grade on admission, defined as a WFNS or H&H grade 1–3; 2) the presence or absence of LOC at ictus; and 3) data on functional outcomes, as evaluated with the modified Rankin Scale, Glasgow outcome scale (GOS), and/or extended GOS at different serial time points.<sup>15</sup>

Because poor neurologic grade, defined as WFNS or H&H grade 4–5, is a strong predictor of poor outcome, this acts as a notable confounder when attempting to evaluate the role of LOC as an independent prognostic factor.<sup>5,16</sup> Furthermore, patients with a poor neurologic grade are often unconscious by definition. A poor neurologic grade is a one-time designation assigned to patients on presentation, whereas LOC, depending on how it is defined, can occur before admission and at any time after initial presentation to the hospital. Therefore, to control for this, we limited our analysis to patients with a good neurologic grade on presentation as defined above.<sup>17-21</sup>

Only one dataset was eligible for our study in terms of meeting our foregoing inclusion criteria. This dataset was from the British Aneurysm Nimodipine Trial (BRANT), a double-blind, placebo-controlled randomized trial of the effect of nimodipine in the prevention of DCI reported by Pickard et al.<sup>22</sup> The BRANT remains one of the most highly cited works on aneurysmal SAH and has

provided the basis for the current use of nimodipine post-SAH as the standard of care.<sup>23</sup> Details of the BRANT are summarized below.

### Clinical Assessment

A post hoc analysis was performed on the 554 patients enrolled in the BRANT, recruited from 4 neurosurgical units in the United Kingdom. A total of 1115 patients were initially admitted to participating centers between June 1985 and September 1987 with SAH diagnosed by lumbar puncture or computed tomography scan. Patients who presented more than 96 hours after SAH were excluded. Other exclusion criteria were pregnancy; major renal, hepatic, or pulmonary disease; preexisting cardiac decompensation; myocardial infarction within the previous 6 months; age <18 years; prior SAH in the previous week resulting in coma; and inability to obtain consent. Eligible patients were assigned a WFNS neurologic grade and were randomized to receive either placebo or 60 mg of nimodipine every 4 hours for 21 days. Study endpoints were incidence of cerebral infarction, ischemic neurologic deficits, and outcome at 3 months after enrollment.<sup>22</sup> LOC in the BRANT-SAHIT dataset was broadly defined as occurrence of unresponsiveness at the onset of SAH.

### Outcomes

The primary outcome for our post hoc analysis was the 5-point GOS as a measure of functional outcome, with a score of 1–3 designated as unfavorable (i.e., death, vegetative state, and severe disability precluding the ability to live independently, respectively).<sup>22</sup> Outcome assessment at the 3-month follow-up was conducted in person by a physician not involved in the patient's initial early management or through mail or telephone interview if a patient was directly unavailable or had relocated out of the region.

Secondary outcomes were DCI, time to DCI, aneurysmal rebleed, length of hospital stay, and time to death. Rebleed or DCI in the trial was categorized as either “definitive” if confirmatory evidence of a bleed or infarct was present on computed tomography scan, during surgery, or during autopsy, or “probable” if based solely on clinical factors and suspicion. For our analysis, only definitive evidence of DCI and rebleed were included.

### Statistical Analysis

For analysis, we used a propensity score-matching algorithm with LOC at the ictus of SAH as the dichotomous exposure cohort. Covariates balanced between the 2 cohorts (LOC present vs. absent at ictus) included age, sex, history of hypertension, history of cardiac disease, WFNS grade, motor deficits, hypertension at admission (defined as systolic blood pressure  $\geq 140/90$  mmHg), treatment cohort (placebo vs. nimodipine), and time from SAH to aneurysm surgery. We used caliper matching in our analysis, with caliper width equal to 0.25 times the standard deviation of the logit of the propensity score, with a 1:1 match ratio between the LOC present and LOC absent cohorts. Previous work by Austin has shown that calipers of a width close to 0.2 minimizes the mean squared error of the estimated treatment effect and eliminates bias in the estimator to produce confidence intervals (CIs) with the appropriate coverage rates.<sup>24</sup> Balance between the covariates in the 2 cohorts used in matching was assessed by plotting propensity

score distribution histograms. All statistical analyses were performed using R statistical software.<sup>25</sup> Continuous variables were compared using a 2-tailed t test. Proportions were compared using the Fisher exact test unless stated otherwise. A P value <0.05 was considered to indicate statistical significance.

## RESULTS

Application of the propensity score-matching algorithm identified a total of 336 patients, including 168 with LOC at the ictus of SAH (LOC cohort) and 168 without LOC at the ictus of SAH (no-LOC cohort). **Table 1** presents the baseline characteristics of the 2 cohorts. There was no statistically significant difference between the cohorts in terms of age, sex, history of hypertension, history of cardiac disease, WFNS grade, motor deficits and hypertension on admission, treatment with nimodipine (60 mg every 4 hours) or placebo, and time from SAH to surgery (aneurysm clipping).

The baseline characteristics of the patients in our analysis are in keeping with previously reported demographics of aneurysmal SAH in terms of average age and female predominance.<sup>26</sup> The majority of patients (69% in each cohort) presented in WFNS grade 2, followed by WFNS grade 3 (30% in each cohort). Only

2 patients in each cohort were classified as WFNS grade 1. Motor deficits were uncommon in both cohorts, and the rate did not differ significantly between cohorts (11% in the LOC cohort vs. 7% in the no-LOC cohort). Approximately one-half of the patients in each cohort received nimodipine, and the other half received placebo. The proportion of patients with angiography-proven aneurysm was similar in the 2 cohorts.

## Primary Outcomes

**Table 2** presents data on our primary and secondary outcomes of interest. The proportion of patients with poor outcome at 3 months (death, vegetative state, or severe disability) was significantly higher in the LOC cohort compared with the no-LOC cohort (30% vs. 19%; odds ratio [OR], 1.78; 95% confidence interval [CI], 1.07–2.94; P = 0.02). There was a trend toward higher mortality in the LOC cohort, but the difference was not statistically significant (19% vs. 13%; OR, 1.54; 95% CI, 0.86–2.7; P = 0.14).

## Secondary Outcomes

There was no statistically significant difference in the incidence of DCI between the 2 cohorts (20% in the LOC cohort vs. 18% in the no-LOC cohort; OR, 1.16; 95% CI, 0.67–2.01; P = 0.677). DCI occurring early after SAH has been associated with worse outcomes; however, there was no significant difference in the time to DCI between the 2 cohorts. Similarly, there was no statistically significant difference in the aneurysm rebleed rate between the 2 cohorts (10% in the LOC cohort vs. 9% in the no-LOC cohort; OR, 1.14; 95% CI, 0.54–2.83; P = 0.853).

Both cohorts had a comparable median time to death (12 days in the LOC cohort vs. 10 days in the no-LOC cohort). Similarly, there was no significant difference in the duration of hospital stay

**Table 1.** Baseline Patient Characteristics Stratified by LOC at Ictus

Variable	LOC at Ictus	
	Present (n = 168)	Absent (n = 168)
Age, years, mean ± SD	49.8 ± 11.7	47.4 ± 12.4
Sex, number (%)		
Male	64 (38.1)	62 (36.9)
Female	104 (61.9)	106 (63.1)
History of hypertension, number (%)	22 (13.1)	14 (8.3)
History of cardiac disease, number (%)	3 (1.8)	3 (1.8)
WFNS grade, number (%)		
I	2 (1.2)	2 (1.2)
II	116 (69.0)	116 (69.0)
III	50 (29.8)	50 (29.8)
Motor deficits at admission, number (%)	19 (11.3)	12 (7.1)
Hypertension at admission, number (%)	25 (14.9)	19 (11.3)
Treatment group, number (%)		
Placebo	88 (52.4)	80 (47.6)
Nimodipine	80 (47.6)	88 (52.4)
Proven aneurysm on angiography, number (%)	126 (75.0)	129 (76.7)
Time from SAH to aneurysm surgery, days (median, IQR)	7 (5–11)	8 (5–15)

LOC, loss of consciousness; SD, standard deviation; WFNS, World Federation of Neuro-surgical Societies; SAH, subarachnoid hemorrhage; IQR, interquartile range.

**Table 2.** Primary and Secondary Outcomes for Patients Stratified by LOC at Ictus

LOC at Ictus			
Variable	Present (n = 168)	Absent (n = 168)	P Value
Primary outcomes, number (%)			
GOS 1—3	51 (30.4)	33 (19.6)	0.023*
GOS 1 (mortality)	33 (19.6)	23 (13.7)	0.145
Secondary outcomes, number (%)			
DCI	34 (20.2)	30 (17.9)	0.677
Time to DCI, days, median (IQR)	6 (5—9)	7 (4—11)	0.958
Rebleed, number (%)	17 (10.1)	15 (8.9)	0.853
Time to death, days, median (IQR)	12 (8—19)	10 (7—21)	0.451
Length of hospital stay, days, median (IQR)	16 (11—22)	15 (10—22)	0.632
LOC, loss of consciousness; GOS, Glasgow outcome scale; DCI, delayed cerebral ischemia; IQR, interquartile range.			
*Denotes significance at <i>P</i> < 0.05.			

between the 2 cohorts (16 days in the LOC cohort vs. 15 days in the no- LOC cohort).

## DISCUSSION

Our findings show that LOC at the ictus of SAH is associated with worse functional outcomes, as evaluated by the GOS at 3 months post-SAH. There was also a trend toward increased mortality in the LOC cohort. Previous studies have shown that LOC following SAH has been associated with worse H&H and WFNS neurologic grades, increased frequency of pulmonary edema, and worse left ventricular function. Radiographically, LOC has been associated with increased cisternal and intraventricular blood, global cerebral ischemia, intraparenchymal blood, hydrocephalus, and acute cerebral infarct. In terms of outcome, more patients in the LOC cohort had poor functional outcome scores compared with the no-LOC cohort at the 3-month and 12-month follow-ups after discharge.<sup>6</sup>

Of note is our finding of no association between LOC at ictus and the development of DCI. This is contrary to a previous study reported by Hop et al.<sup>8</sup> in 125 patients, which found an increased risk of DCI in patients who experienced LOC for >1 hour after SAH. A potential confounding factor in the Hop et al. study may have been the inclusion of patients with a poor neurologic grade (i.e., WFNS  $\geq 4$  or H&H  $\geq 4$ ) on presentation, because these patients may be considered unconscious by definition, and a worse clinical grade is a known independent risk factor for the development of subsequent DCI. Nonetheless, our results are in agreement with results reported by Suwatcharakoon et al.<sup>6</sup> in a retrospective analysis of 1460 patients with SAH, which also failed to find an association between LOC and subsequent DCI after controlling for other prognostic variables, including age, neurologic grade on admission, aneurysm size, and physiological derangements on admission, such as hypertension.

The cause of LOC in SAH has been thought to be associated with decreased cerebral perfusion pressure (CPP) in the face of increased intracranial pressure (ICP).<sup>6,27</sup> The mechanism of the increased ICP in SAH has yet to be fully elucidated, but is thought to be due to a combination of hemorrhage volume, vasoparalysis, and decreased cerebrospinal fluid resorption.<sup>28</sup> Similarly, the development of hydrocephalus, seizures, and cardiopulmonary dysfunction following SAH also may contribute to increased ICP.<sup>5</sup> Even transient decreases in CPP can cause global cerebral ischemia, contributing to early brain injury (within 72 hours of SAH ictus), believed to be a main contributor to morbidity in patients with SAH.<sup>28</sup> Various contributory apoptotic cascades, including caspase-dependent and mitochondrial caspase-independent pathways, have been implicated, leading to disruption of the blood-brain barrier, brain edema, cell death, and necrosis.<sup>5,28-30</sup> The mechanism of early brain injury described above in relation to LOC also has been thought to be pathophysiologically distinct in several ways from late or delayed injury due

to vasospasm.<sup>29</sup> This also may explain in part the lack of association between initial LOC and the subsequent development of DCI during the course of recovery.

Previous studies of LOC following SAH have all been subject to the same limitation of suboptimal reliability in terms of accurate reporting of LOC either by the patient himself or herself (particularly if he or she presents with a poor neurologic grade and is stuporous or unreliable) or by witnesses. Although limited by practicality, future studies should attempt to more accurately assess the presence of LOC through collateral historians and subsequently note the LOC of presenting patients at multiple, different serial time points early on. This will also allow more robust analysis of the true effect of varying durations of LOC on outcome. In addition, a standardized definition of LOC needs to be established to improve interobserver reliability. Patients in whom a history of LOC is equivocal may be excluded. The performance of early electrocardiographic and electroencephalographic monitoring may be able to better delineate the etiology of LOC if caused by cardiac arrhythmias or epileptogenic activity.<sup>6</sup> Additional work also may focus on the effects of SAH on the brain, separating the direct cytotoxic effect of blood on the brain and the indirect effects of increased ICP leading to decreased CPP. The cellular mechanisms and pathways associated with LOC and early brain injury, including the identification of molecular markers or targets for the potential design of future therapeutics, remain to be further elucidated.

A main limitation of the present study is that our post hoc analysis was done in patients recruited between 1985 and 1987 for the BRANT. Care for patients with aneurysmal SAH has since improved, with better outcomes reported in more recent studies. Patient information, including clinical information on admission, including the presence of confounders such as syncope, seizures, or cardiac arrest, was limited. Furthermore, radiographic data on the location and size of the aneurysms were unavailable. In addition, the duration of LOC was not recorded completely.

## CONCLUSION

Overall, our study reaffirms the prognostic role of LOC at the ictus of aneurysmal SAH in portending poor outcomes. LOC may be an indicator of early brain injury and an independent predictor of poor neurologic outcome independent of the neurologic grade of patients on presentation. Future directions should focus on refining the definition, verification, and monitoring of LOC in SAH and determining the association between the duration of LOC and outcomes post-SAH.

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## APPENDIX

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